REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-24 were previously pending in this application. Claims 1, 8 and 10 have been amended above. New claim 245 has been added. No claimes have been canceled by this paper. Accordingly, claims 1-24 and 245 are presented for further examination.

The first page (line 1) of the specification has been amended by inserting information cross-referencing this application with the prior parent application, Serial No. 08/574,443, filed on December 15, 1995. The parent application was revived for purposes of continuity so that the present continuation application could be filed. Hence, the parent application (Serial No. 08/574,443) should now be abandoned, and that has been indicated in the amendment to the specification above. Applicants wish to point out that an office action was apparently issued in Serial No. 08/574,443 on February 19, 1999. The present Examiner is listed as handling that application. It is Applicants' intention to file a communication in Serial No. 08/574,443 indicating that that application was abandoned in favor of the present continuation.

For the sake of clarity and definiteness, relatively minor changes to the claims have been effected above. First, claim 1 has been amended to read "[a] non-native polynucleotide construct comprising at least one sequence segment, which construct when present in a cell produces a product, said construct comprising at least one member selected from the group consisting of a modified nucleotide, a nucleotide analog or a non-nucleic acid entity, and a combination of the foregoing." Second, new claim 245 has been added, that claim reciting "[t]he construct of claim 3, wherein said sequence segment is in double-stranded form." Finally, the dependencies in claims 8 and 10 have been changed to claims 7 and 245, respectively.

No new matter is believed to be inserted by the above amendments to the claims or by the addition of new claim 245. All of the foregoing changes

to the claims is believed to enhance the clarity of Applicants' claimed invention. Entry of the amendments and new claim are respectfully requested.

Objection to Patent Drawings

Acknowledgement is made of the Notice of Draftperson's Patent Drawings Review that was issued on January 22, 1999. Formal drawings will be submitted as soon as allowable subject matter has been indicated in this application.

Submission of Sequence Listing

Applicants are filing concurrently with this Amendment a response to the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The Rejection for Double Patenting Under 35 U.S.C. §101

Claims 2-24 stand provisionally rejected under 35 U.S.C. §101 as claiming the same invention of claims 2-24 of copending Application Nos.: 08/978633, 08/978634, 08/978635, 08/978636, 08/978637, 08/978638, and 08/978639. In the February 3, 1999 Office Action (page 3), the Examiner noted that "[t]his is a provisional double patenting since the conflicting claims have not in fact been patented."

Applicants' undersigned attorney has examined the filings of the various divisional applications cited by the Examiner in the double patenting rejection who astutely observed that claims 2-24 were still pending in other related divisional applications. It is believed that pending claims 2-24 were inadvertently included in the divisional filings and not canceled as Applicants intended. In any case, it is Applicants' intention to maintain a line of

demarcation between the present claims and any of the claims in the related divisional applications. Such a line will be maintained in part by canceling claims 2-24 in those other divisional applications, either in responding to any outstanding office actions or by filing a second preliminary amendment. In the meantime, it is respectfully requested that the double patenting rejection be held in abeyance until claims 2-24 are canceled in the divisional applications.

The Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1-24 stand rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the February 3, 1999 Office Action (page 3), the Examiner stated:

> Claims 1-21 are drawn to "a non-naturally occurring construct." The metes and bounds of said construct are not defined because the scope of "non-natural" is not known. The same applies to the language "non-natural entity... and combination."
>
> Claim 8 lacks antecedent basis for "chemical modification."
>
> In claim 10, the language "attached to a single strand or to both strands of said sequence segment" is vague because the structure in light of the construct in claim 1 is not clearly defined, and there is no antecendent basis for "said sequence segment."
>
> In claims 2 and 3, the language "portion" is vague because the structure in light of the construct in claim 1 is not clearly defined.

The indefiniteness rejection is respectfully traversed.

As indicated in the opening remarks of this Amendment, claim 1 has been amended to recite "a non-native polynucleotide construct." This language is accepted under U.S. patent practice having been recited in the claims of at least two duly issued U.S. patents. See, for example, Inouye et al., U.S. Patent No. 5,272,065, issued on December 21, 1993; and Donohue et al., U.S. Patent No. 5,747,328, issued on May 5, 1998. Copies of the aforementioned U.S. Patents Nos. 5,272,065 and 5,747,328 are attached as Exhibits A and B, respectively. See in particular claims 1, 26, 50, 73, 96 and 122 ("non-native polynucleotide construct") in the '065 Patent (Exhibit

A). See in particular claim 9 ("non-native genetic construct") in the '328 Patent (Exhibit B).

With respect to the language "non-nucleic acid entity" in claim 1, it is believed that this term is well-defined in Applicants' disclosure. In the middle paragraphs on page 36, for example, Applicants define the "non-nucleic acid entity" thusly:

> The non-nucleic acid entity or entities may take any number of diverse forms. These include natural polymers, synthetic polymers, natural ligands and synthetic ligands, as well as combinations of any and all of the foregoing. When the non-nucleic acid entity or entities take the form of a natural polymer, suitable members may be modified or unmodified. Natural polymers can be selected from a polypeptide, a protein, a polysaccharide, a fatty acid, and a fatty acid ester as well as any and all combinations of the foregoing.
>
> When the present invention contemplates the use of a synthetic polymer for the non-nucleic acid entity or entities, homopolymers and heteropolymers may be employed. Such homopolymers and heteropolymers arae in many ways preferred when they carry a net negative charge or a net positive charge.

There are other portions in the specification that also describe the "non-nucleic acid entity" recited in claim 1. In view of Applicants' disclosure which is replete with descriptions of the instantly recited "non-nucleic acid entity," the language of claim 1 is believed to pass the statutory strictures for definiteness.

As also indicated above, claim 8 now properly depends from claim 7 and not claim 6 as originally filed. Claim 7 refers to the "modified nucleotide" of claim 1 and to the embodiment where such modified nucleotide "has been chemically modfieid." Hence, a proper antecedent basis has now been provided for the term "chemical modification" in claim 8.

The dependency in claim 10 has been changed to new claim 245, that claim being directed to "[t]he construct of claim 3, wherein said sequence segment is in double-stranded form." In turn, claim 3 depends from claim 1, and recites "wherein said construct or a portion thereof is single-stranded, double-stranded, partially double-stranded or triple-stranded." As amended

above, claim 1 recites "[a] non-naturally occurring non-native polynucleotide construct comprising at least one sequence segment . . ." Hence, the subject matter of claim 10 with respect to "said sequence segment" now enjoys a proper antecedent basis in prior claims to which claim 10 now refers.

With respect to the language "portion" in claims 2 and 3, it is believed that in view of the above amendments to claim 1, this ground of rejection has been obviated.

In light of the above changes to the claims, it is respectfully requested that the rejection of claims 1-24 under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

The Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1-24 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the Office Action (pages 4-6), the Examiner stated:

> The construct as taught in the claims broadly encompasses a multitude of constructs for use in a cell to produce a product, the construct comprising at least one modified nucleotide, a nucleotide analog or a non-nucleic acid entity, or a combination of those. The limitations which further define the construct also do so broadly by specifying (1) the construct as linear or circular, (2) the construct as comprising 1,2 or 3 strands, (3) comprising a terminus, a polynucleotide tail which can hybridize, (4) composed of RNA or DNA or combinations, (5)containing chemically modified nucleotides or analogs, (6) containing non-nucleic acid entities composed of polymers or ligands or a combination, (7) further specifying the natural and synthetic polymers, the synthetic homo- or heteropolymer with a net charge, (8)the construct imparting a "further biological activity" by the modified nucleotide, analog, entity, ligand or combination of those, further defined as nuclease resistance, cell recognition, cell binding, and cellular or nuclear localization or a combination, (9) a ligand attached to one of the modified nucleotides, etc. of claim1, further described as attached to a "segment" or "tail" of the construct , and further defined as being a macromolecule or small molecule or

combination. Claims 22-24 describe a second construct "which when present in a cell produces a product, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand."

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences and/or proteins to perform a biological function such as antisense inhibiton of a product. Antisense inhibition of an HIV protein is exemplified in cell culture by use of a modified expression vector construct. The claimed invention thus reads on constructs in cells and whole organisms, but is not enabled for such use in whole organisms.

There is a high level of unpredictability known in the antisense art for *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo,* the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Note Flanagan et al. who teach "although numerous reports have cited antisense effects using oligonucleotides added to cell medium, direct proof that oligonucleotides enter cells and affect gene inhibition by an antisense mechanism is still lacking (page48, column 1)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro,* antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo,* effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* in view of the lack of guidance in the specification and the unpredictability in the art. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo,* (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked

by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of teaching of these factors in inhibition of the target, coupled to the amount of "trial and error" experimentation involved in the deduction of these results would lead one skilled in the art to necessarily practice an undue amount of experimentation *in vivo*.

The enablement rejection is respectfully traversed.

Applicants respectfully contend that their disclosure describes the claimed subject matter such that one skilled in the art could make and use same without undue experimentation. It is further contended that the state of the art of construct technology in biological systems at the time this application was originally filed in 1995 had become predictable enough so that the skilled artisan could have practiced Applicants' claimed invention, again, without any undue experimentation.

Reconsideration and withdrawal of the enablement rejection are respectfully requested.

The Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1-24 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the Office Action (page 7), the Examiner stated:

> See description of the claimed invention and specification *supra*.
> It is not clear from the specification as filed that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. The written description guidelines teach an inverse correlation between the level of predictability in the art and the satisfactory written description in the specification to support a broad genus as claimed.
> The instant specification describes in theory a number of potential modified nucleic acid constructs for use in expression of an entity in a cell. The supporting figures provide limited additional disclosure of relevant identifying structural characteristics. The claims, however, broadly encompass "non-naturally occurring ... construct(s)," the whole genus of which, or even representative

species of which, are not represented by the disclosure as filed so that one of skill in the art could reasonably identify all the members. For example, the figures primarily correspond to expression vector based constructs which are only one facet of the invention as claimed.

See the June 15, 1998 (Vol. 63, No. 114, Pages 32639-32645) Federal Register for the interim guidelines for the examination of patent applications under the 35 U.S.C. 112 "Written Description" requirement.

Notwithstanding the new guidelines published in June 1998, Applicants continue to believe that the operative words in the written description requirement continue to be "reasonably conclude," that is to say, that one skilled in the art can reasonably that the inventor had possession of the claimed invention.

Viewed under that classical standard, it is believed that the present claims are adequately described in the specification so as to meet the statutory requirements for written description.

Reconsideration and withdrawal of the written description rejection are respectfully requested.

The First Rejection Under 35 U.S.C. §102

Claim 1 stands rejected under 35 U.S.C. 102(b) as being anticipated by Hsiung et al., U.S. Patent No. 4,795,706, issued on January 3, 1989. In the Office Action (page 8), the Examiner stated: "Hsiung et al. teach a vector incorporating syntesized nucleotide sequences for expression of the synthesized sequences in a cell."

The anticipation rejection by Hsiung et al. is respectfully traversed.

Applicants respectfully contend that there is a lack of identity of material elements between their instantly claimed invention and Hsiung's disclosure. More specifically, Hsiung et al. do not disclose or suggest that their construct should comprise at least one member recited in the Markush language of claim 1, namely, a modified nucleotide, a nucleotide analog or a non-nucleic acid entity.

Reconsideration and withdrawal of the anticipation rejection are respectfully requested.

The Second Rejection Under 35 U.S.C. §102

Claims 1-24 stand rejected under 35 U.S.C. §102(e) as being anticipated by Meyer et al., U.S. Patent No. 5,574,142, issued on November 12, 1996. In the Office Action (page 8), the Examiner stated:

> Meyer et al. teach a covalently linked conjugate of an oligonucleotide (ODN) with a peptide and a carrier or targeting ligand (ODN-peptide-carrier) including a therapeutic oligonucleotide which is capable of selectively binding to a target sequence of DNA, RNA or protein inside a target cell. The invention of Meyer et al. reads on all of the instant claimed limitations (see description of claimed invention above) for a non-naturally occuring construct for production of a product in a cell (in Meyer, an antisense oligonucleotide is produced).

The anticipation rejection by Meyer et al. is respectfully traversed.

It is respectfully contended that Meyer's patent neither discloses nor suggests Applicants' claimed invention. Reconsideration and withdrawal of this anticipation rejection is respectfully requested.

The Third Rejection Under 35 U.S.C. §102

Claim 1 stands rejected under 35 U.S.C. §102(e) as being anticipated by Carter et al., U.S. Patent No. 5,587,308, issued on December 24, 1996. In the Office Action (page 9), the Examiner stated "Carter et al. teach a modified recombinant DNA constrruct of expression of foreign genes in fusion with a synthetic sequence contained in the vector in a cell and therefore reads on the limitations of instant claim 1."

The anticipation rejection by Carter et al. is respectfully traversed.

It is believed that Carter's disclosure does not anticipate the present invention set forth in claim 1 because the former fails to meet the claim limitation with respect to the construct comprising at least one member selected from the group consisting of a modified nucleotide, a nucleotide analog or a non-nucleic acid entity, and a combination of the foregoing.

Reconsideration and withdrawal of the third anticipation rejection are respectfully requested.

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SUMMARY AND CONCLUSIONS

Claims 1-24 and 245 are being presented for further examination, claims 1, 8 and 10 having been amended and new claim 245 having been added.

The small entity fee for adding new dependent claim 245 is $9.00, authorization for which has been made in the accompanying transmittal form. Small entity status was previously established in this application and is still application. In addition, this Amendment is being accompanied by a Request For An Extension Of Time (3 months) and authorization for the small entity fee therefor. No other fee or fees are believed due for filing this Amendment. In the event that any other fee or fees are due, authorization is hereby given to charge the amount of any such other fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

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